PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 1781
Donna E. Prunkard, et al.	Examiner: D. Crouch
Application No.: 09/232,488	Art Unit: 1632
Filed: January 15, 1999	DECLARATION OF JEFF LANDES
For: PRODUCTION OF FIBRINOGEN IN TRANSGENIC ANIMALS	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jeff Landes, state as follows:

(1) I am currently employed as a senior patent attorney at ZymoGenetics, Inc. (ZymoGenetics).

(2) I assumed responsibility on behalf of ZymoGenetics for the above-captioned application on July 7, 2007, when I assumed the project from Gary Parker, a Senior Patent Agent, who had retired from the company.

(3) The named inventors of the current application, Donald Foster and Donna Prunkard, are or were employees of ZymoGenetics, Inc.

(4) I understand that Donna Prunkard was laid off from ZymoGenetics December 31, 2006.

(5) Prior to my assuming responsibility for the application, I understand that Gary Parker and Joe Liebeschuetz (outside counsel prosecuting the application) had previously been in contact with Donna Prunkard regarding signing the declaration in the above case, but that Donna Prunkard had not done so, because she said that she had concerns whether she was a co-inventor of the claims in their currently amended form, in particular with respect to the phrase relating to the three fibrinogen sequences being part of the same vector ("same vector" element).

(6) On assuming responsibility for the case, I conducted an evaluation of the inventorship of the current claims and concluded that Donna Prunkard was a co-inventor of the pending claims. In brief, the reason for my conclusion was that joint inventors need not work together, make the same type/amount of contribution or contribute to all of the subject matter of the claims. So, irrespective whether Donna Prunkard was personally responsible for the "same vector" element of the claims, her contribution to, for example, the gene cloning and to the development of the expression vectors was sufficient to make her a co-inventor of the pending claims.

(7) On August 15, 2007, I had a telephone conversation with Donna Prunkard. In that phone conversation I discussed with her that we have made a legal determination that she is an inventor of the current claims. Donna Prunkard stated that she did not make the triple insert vector; however, Donna Prunkard also stated that she was responsible for cloning the three fibrinogen genes and generating the three single insert vectors, amongst other things. I then stated to Ms. Prunkard that it is our legal determination that this same invention is embodied in the current claims. I told Ms. Prunkard that I would re-send to her a copy of the instant claims and her declaration.

(8) On August 20, 2007 I sent to Donna Prunkard by certified mail a copy of the original claims, the re-issue claims as filed, the amended claims, and the declaration she was being requested to sign. A copy of my cover letter is attached as Exhibit A. I understand Donna Prunkard had already reviewed a copy of the specification (see paragraph (3) of her declaration dated January 13, 1999 filed with the application).

(9) On August 29, 2007, I received a reply from Donna Prunkard by email that she continued to have concerns regarding whether she was a co-inventor because of the "same vector" feature in the claims.

(10) I replied to this email on September 4, 2007. In my reply, I reiterated the basis for determining that Donna Prunkard was an inventor and requested that she return the declaration by September 12, 2007, and stated that a failure to do so would be construed as a refusal to sign. A copy of the email exchange referred to in paragraph (9) and this paragraph (10) is attached as Exhibit B.

(11) I have not received a reply to my email of September 4, 2007 and conclude that Donna Prunkard has refused to sign her declaration and further attempts to obtain Donna Prunkard's signature would be futile.

Respectfully submitted,

By: _____ Date December 13, 2007
Jeff Landes

Registration Number 55,355

ZYMOGENETICS

EXHIBIT A

August 20, 2007

Direct Dial: (206) 442-3727
Facsimile: (206) 442-6678

Via Certified Mail
Donna E. Prunkard
1463 NW 92nd Ave.
Seattle, WA 98117

Re: Reissue Application from U.S. Patent No.: 5,639,940
Application Serial No.: 09/232,488
Production of Fibrinogen in Transgenic Animals
Our Ref. 93-15R1

Dear Donna:

Enclosed, please find the documents that we discussed by phone on August 15th, 2007:

- Cover letter from Gary Parker, addressed to you and dated February 15th, 2007;
- Claims from original patent;
- Claims filed in re-issue case;
- Claims now pending; and
- Declaration of Inventorship.

Please review, sign and return the enclosed Declaration of Inventorship at your soonest convenience, but no later than August 31, 2007. A addressed and postmarked return envelope is enclosed.

Thank you for your assistance with this matter. If you have any questions or comments, please feel free to contact me at (206) 442-3727 (direct dial) or (206) 442-6678 (facsimile).

Sincerely,

Jeff Landes, Esq.
Senior Patent Attorney

Enclosures

ZYMOGENETICS

February 15, 2007

Donna E. Prunkard
1463 NW 92nd Street
Seattle, WA 98117

Re: U.S. Patent Application No. 09/232,488
PRODUCTION OF FIBRINOGEN IN TRANSGENIC ANIMALS
Our Ref. 93-15R1

Dear Donna:

Enclosed is the supplemental reissue declaration that we discussed, together with copies of the claims of the original granted patent, the claims filed in the reissue application, and the claims now pending. The reissue and pending claims are marked to show changes over the claims of the granted patent. Added text is indicated by underlining, and deleted text is within square brackets. As you will see, the pending claims are now being amended to specify that the three fibrinogen genes are contained in a single vector, and to include the use of early stage embryos.

Please review these materials and, if you agree with the statements made in the declaration, sign and date it where indicated. A return envelope is enclosed.

If you have any questions or concerns, please give me a call (442-6673).

Thank you very much for your cooperation on this matter.

Best regards,

Gary Parker
Principal Patent Agent
Senior Patent Fellow

encl.

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-continued

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(v i i) IMMEDIATE SOURCE:
(B) CLONE: zc6515

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GGGTTTCTAG CCCTACTAGT AG 22

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:27:

AAGCTACGCG TCGATCGTCT AGAGTATATC GTCGACGCGT CGATCGG 47

We claim:

1. A method for producing biocompetent fibrinogen comprising:

providing a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain, a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, and a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, wherein each chain is from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal;

introducing said DNA segments into a fertilized egg of a non-human mammalian species heterologous to the species of origin of said fibrinogen chains;

inserting said egg into an oviduct or uterus of a female of said mammalian species to obtain offspring carrying said DNA segments;

breeding said offspring to produce female progeny that express said first, second and third DNA segments and produce milk containing biocompetent fibrinogen encoded by said segments;

collecting milk from said female progeny; and

and recovering the biocompetent fibrinogen from the milk.

2. A method according to claim 1 wherein said species into which said DNA segments are introduced is selected from the group consisting of sheep, pigs, goats, and cattle.

3. A method according to claim 1 wherein each of said first, second and third DNA segments comprises an intron.

4. A method according to claim 1 wherein the molar ratio of said first, second and third DNA segments is within the range of 0.5–1:0.5–1:0.5–1.

5. A method according to claim 1 wherein each of said first, second and third DNA segments is operably linked to a transcription promoter selected from the group consisting of casein, β-lactoglobulin, α-lactalbumin and whey acidic protein gene promoters.

6. A method according to claim 1 wherein said first, second and third DNA segments are expressed under the control of a β-lactoglobulin promoter.

7. A method according to claim 1 wherein said introducing step comprises injecting said first, second and third DNA segments into a pronucleus of said fertilized egg.

8. A method according to claim 1 wherein said fibrinogen is human fibrinogen.

9. A method according to claim 1 wherein said second DNA segment comprises a sequence of nucleotides as shown in SEQ ID NO: 3 from nucleotide 470 to nucleotide 8100.

10. A method according to claim 1 wherein said second DNA segment comprises a sequence of nucleotides as shown in SEQ ID NO: 3 from nucleotide 512 to nucleotide 8100.

11. A method according to claim 1 wherein said species into which said DNA segments is introduced is sheep.

12. A method of producing biocompetent fibrinogen comprising:

incorporating a first DNA segment encoding a secretion signal operably linked to an Aα chain of fibrinogen into a β-lactoglobulin gene to produce a first gene fusion comprising a β-lactoglobulin promoter operably linked to the first DNA segment;

incorporating a second DNA segment encoding a secretion signal operably linked to a Bβ chain of fibrinogen into a β-lactoglobulin gene to produce a second gene fusion comprising a β-lactoglobulin promoter operably linked to the second DNA segment;

incorporating a third DNA segment encoding a secretion signal operably linked to a γ chain of fibrinogen into a β-lactoglobulin gene to produce a third gene fusion comprising a β-lactoglobulin promoter operably linked to the third DNA segment wherein each of said first, second and third segments are of the same species;

introducing said first, second and third gene fusions into the germ line of a non-human mammal so that said DNA segments are expressed in a mammary gland of

said mammal or its female progeny and biocompetent fibrinogen is secreted into milk of said mammal or its female progeny;

obtaining milk from said mammal or its female progeny; and

recovering said fibrinogen from said milk.

13. A method according to claim 12 wherein said mammal is a sheep, pig, goat or cow.

14. A method according to claim 12 wherein each of said first, second and third gene fusions comprises an intron.

15. A method according to claim 12 wherein the molar ratio of said first, second and third gene fusions introduced is within the range of 0.5–1:0.5–1:0.5–1.

16. A method according to claim 12 wherein said introducing step comprises injecting said first, second and third gene fusions into a pronucleus of a fertilized egg and inserting said egg into an oviduct of a pseudopregnant female to produce female offspring carrying said gene fusions in the germ line, wherein said egg and said pseudopregnant female are of the same species.

17. A method according to claim 12 wherein said mammal is a sheep.

18. A method for producing biocompetent fibrinogen comprising:

providing a transgenic female non-human mammal carrying in its germline heterologous DNA segments encoding Aα, Bβ and γ chains of fibrinogen, wherein said segments are expressed in a mammary gland of said mammal and biocompetent fibrinogen encoded by said segments is secreted into milk of said mammal;

collecting milk from said mammal; and

recovering said biocompetent fibrinogen from said milk.

19. A method according to claim 18 wherein said mammal is a sheep, pig, goat or cow.

20. A method according to claim 18 wherein said mammal is a sheep.

21. A transgenic non-human female mammal that produces recoverable amounts of biocompetent human fibrinogen in its milk, wherein said mammal comprises:

a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain,

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, and

a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, and

further wherein each chain is derived from the same species and is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal.

22. A mammal according to claim 21 wherein said mammal is a sheep.

23. A process for producing a transgenic offspring of a mammal comprising:

providing a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain, a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, and a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, wherein each chain is derived from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal;

introducing said DNA segments into a fertilized egg of a non-human mammalian species heterologous to the species of origin of said fibrinogen chains;

inserting said fertilized egg into an oviduct or uterus of a female of said mammalian species; and

allowing said fertilized egg to develop thereby producing transgenic offspring carrying said first, second and third DNA segments, wherein female progeny of said mammal express said DNA segments in a mammary gland to produce biocompetent fibrinogen.

24. A process according to claim 23 wherein said offspring is female.

25. A process according to claim 23 wherein said offspring is male.

26. A non-human mammal produced according to the process of claim 23.

27. A non-human mammal according to claim 26 wherein said mammal is female.

28. A non-human female mammal according to claim 27 that produces milk containing biocompetent fibrinogen encoded by said DNA segments.

29. A non-human mammal according to claim 26 wherein said mammal is male.

30. A non-human mammal carrying in its germline DNA segments encoding human Aα, Bβ and γ chains of fibrinogen, wherein female progeny of said mammal express said DNA segments in a mammary gland to produce biocompetent human fibrinogen.

31. A mammal non-human according to claim 30 wherein said mammal is female.

32. A mammal non-human according to claim 30 wherein said mammal is male.

33. A mammal according to claim 30, wherein said mammal is a sheep.

* * * * *

(Claims filed in reissue case)

We claim:

1. A method for producing biocompetent fibrinogen comprising:

providing a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain,

the DNA segment comprising genomic DNA encoding the Aα chain;

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain,

the DNA segment comprising genomic DNA encoding the Bβ chain; and

a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain,

the DNA segment comprising genomic DNA encoding the γ chain,

wherein each chain is from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal;

introducing said DNA segments into a fertilized egg of a non-human mammalian species heterologous to the species of origin of said fibrinogen chains;

inserting said egg into an oviduct or uterus of a female of said mammalian species to obtain offspring carrying said DNA segments;

breeding said offspring to produce female progeny that express said first, second and third DNA segments and produce milk containing biocompetent fibrinogen encoded by said segments;

collecting milk from said female progeny; and

and recovering the biocompetent fibrinogen from the milk.

2. A method according to claim 1 wherein said species into which said DNA segments are introduced is selected from the group consisting of sheep, pigs, goats, and cattle.

3. A method according to claim 1 wherein each of said first, second and third DNA segments comprises an intron.

4. A method according to claim 1 wherein the molar ratio of said first, second and third DNA segments is within the range of 0.5–1:0.5–1:0.5–1.

5. A method according to claim 1 wherein each of said first, second and third DNA segments is operably linked to a transcription promoter selected from the group consisting of casein, β-lactoglobulin, α-lactalbumin and whey acidic protein gene promoters.

6. A method according to claim 1 wherein said first, second and third DNA segments are expressed under the control of a β-lactoglobulin promoter.

7. A method according to claim 1 wherein said introducing step comprises injecting said first, second and third DNA segments into a pronucleus of said fertilized egg.

8. A method according to claim 1 wherein said fibrinogen is human fibrinogen.

9. A method according to claim 1 wherein said second DNA segment comprises a sequence of nucleotides as shown in SEQ ID NO: 3 from nucleotide 470 to nucleotide 8100.

10. A method according to claim 1 wherein said second DNA segment comprises a sequence of nucleotides as shown in SEQ ID NO: 3 from nucleotide 512 to nucleotide 8100.

11. A method according to claim 1 wherein said species into which said DNA segments is introduced is sheep.

12. A method of producing biocompetent fibrinogen comprising:

incorporating a first DNA segment encoding a secretion signal operably linked to an Aα chain of fibrinogen into a β-lactoglobulin gene to produce a first gene fusion comprising a β-lactoglobulin promoter operably linked to the first DNA segment

, the DNA segment comprising genomic DNA encoding the Aα chain;

incorporating a second DNA segment encoding a secretion signal operably linked to a Bβ chain of fibrinogen into a β-lactoglobulin gene to produce a second gene fusion comprising a β-lactoglobulin promoter operably linked to the second DNA segment

, the DNA segment comprising genomic DNA encoding the Bβ chain;

incorporating a third DNA segment encoding a secretion signal operably linked to a γ chain of fibrinogen into a β-lactoglobulin gene to produce a third gene fusion comprising a β-lactoglobulin promoter operably linked to the third DNA segment

, the DNA segment comprising genomic DNA encoding the γ chain,

wherein each of said first, second and third segments are of the same species;

introducing said first, second and third gene fusions into the germ line of a non-human mammal so that said DNA segments are expressed in a mammary gland of

said mammal or its female progeny and biocompetent fibrinogen is secreted into milk of said mammal or its female progeny;

obtaining milk from said mammal or its female progeny; and

recovering said fibrinogen from said milk.

13. A method according to claim 12 wherein said mammal is a sheep, pig, goat or cow.

14. A method according to claim 12 wherein each of said first, second and third gene fusions comprises an intron.

15. A method according to claim 12 wherein the molar ratio of said first, second and third gene fusions introduced is within the range of 0.5–1:0.5–1:0.5–1.

16. A method according to claim 12 wherein said introducing step comprises injecting said first, second and third gene fusions into a pronucleus of a fertilized egg and inserting said egg into an oviduct of a pseudopregnant female to produce female offspring carrying said gene fusions in the germ line, wherein said egg and said pseudopregnant female are of the same species.

17. A method according to claim 12 wherein said mammal is a sheep.

18. A method for producing biocompetent fibrinogen comprising:

providing a transgenic female non-human mammal carrying in its germline heterologous

genomic

DNA segments encoding Aα, Bβ and γ chains of fibrinogen, wherein said segments are expressed in a mammary gland of said mammal and biocompetent fibrinogen encoded by said segments is secreted into milk of said mammal;

collecting milk from said mammal; and

recovering said biocompetent fibrinogen from said milk.

19. A method according to claim 18 wherein said mammal is a sheep, pig, goat or cow.

20. A method according to claim 18 wherein said mammal is a sheep.

21. A transgenic non-human female mammal that produces recoverable amounts of biocompetent human fibrinogen in its milk, wherein said mammal comprises:

a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain.

the DNA segment comprising heterologous genomic DNA encoding the Aα chain;

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain.

the DNA segment comprising heterologous genomic DNA encoding the Bβ chain;

and

a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain.

the DNA segment comprising heterologous genomic DNA encoding the γ chain;

and

further wherein each chain is derived from the same species and is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal.

22. A mammal according to claim 21 wherein said mammal is a sheep.

23. A process for producing a transgenic offspring of a mammal comprising:

providing a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain.

the DNA segment comprising genomic DNA encoding the Aα chain;

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain.

the DNA segment comprising genomic DNA encoding the Bβ chain;

and a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain.

the DNA segment comprising genomic DNA encoding the γ chain,

wherein each chain is derived from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal;

introducing said DNA segments into a fertilized egg of a non-human mammalian species heterologous to the species of origin of said fibrinogen chains;

inserting said fertilized egg into an oviduct or uterus of a female of said mammalian species; and

allowing said fertilized egg to develop thereby producing transgenic offspring carrying said first, second and third DNA segments, wherein female progeny of said mammal express said DNA segments in a mammary gland to produce biocompetent fibrinogen.

24. A process according to claim 23 wherein said offspring is female.

25. A process according to claim 23 wherein said offspring is male.

26. A non-human mammal produced according to the process of claim 23.

27. A non-human mammal according to claim 26 wherein said mammal is female.

28. A non-human female mammal according to claim 27 that produces milk containing biocompetent fibrinogen encoded by said DNA segments.

29. A non-human mammal according to claim 26 wherein said mammal is male.

30. A non-human mammal carrying in its germline

heterologous genomic

DNA

segments encoding human Aα, Bβ and γ chains of fibrinogen, wherein female progeny of said mammal express said DNA segments in a mammary gland to produce bio-competent human fibrinogen.

31. A mammal non-human according to claim 30 wherein said mammal is female.

32. A mammal non-human according to claim 30 wherein said mammal is male.

33. A mammal according to claim 30, wherein said mammal is a sheep.

* * * * *

34. A set of DNA sequences comprising:

a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain, the DNA segment comprising genomic DNA encoding the Aα chain;

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, the DNA segment comprising genomic DNA encoding the Bβ chain; and

a third DNA segment encoding a secretion signal operably linked to a to a heterologous fibrinogen γ chain, the DNA segment comprising genomic DNA encoding the γ chain, wherein each chain is from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal.

(Claims now pending)

Listing of Claims:

1. (twice amended) A method for producing biocompetent fibrinogen comprising:

providing a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain, the DNA segment comprising genomic DNA encoding the Aα chain, a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, the DNA segment comprising genomic DNA encoding the Bβ chain, and a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, the DNA segment comprising genomic DNA encoding the γ chain, wherein each chain is from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal and the first, second, third segments are linked in a single vector;

introducing said DNA segments into an [fertilized] egg or early stage embryo of a non-human mammalian species heterologous to the species of origin of said fibrinogen chains;

inserting said egg or early stage embryo into an oviduct or uterus of a female of said mammalian species to obtain offspring carrying said DNA segments;

breeding said offspring to produce female progeny that express said first, second and third DNA segments and produce milk containing biocompetent fibrinogen encoded by said segments;

collecting milk from said female progeny; and

and recovering the biocompetent fibrinogen from the milk.

2. (original) A method according to claim 1 wherein said species into which said DNA segments are introduced is selected from the group consisting of sheep, pigs, goats, and cattle.

3. (canceled)

4. (canceled)

5. (original) A method according to claim 1 wherein each of said first, second and third DNA segments is operably linked to a transcription promoter selected from the group consisting of casein, β-lactoglobulin, α-lactalbumin and whey acidic protein gene promoters.

6. (original) A method according to claim 1 wherein said first, second and third DNA segments are expressed under the control of a β-lactoglobulin promoter.

7. (amended) A method according to claim 1 wherein said introducing step comprises injecting said first, second and third DNA segments into a pronucleus of said [fertilized] egg or early stage embryo.

8. (original) A method according to claim 1 wherein said fibrinogen is human fibrinogen.

9. (original) A method according to claim 1 wherein said second DNA segment comprises a sequence of nucleotides as shown in SEQ ID NO: 3 from nucleotide 470 to nucleotide 8100.

10. (original) A method according to claim 1 wherein said second DNA segment comprises a sequence of nucleotides as shown in SEQ ID NO: 3 from nucleotide 512 to nucleotide 8100.

11. (original) A method according to claim 1 wherein said species into which said DNA segments is introduced is sheep.

12. (twice amended) A method of producing biocompetent fibrinogen comprising:

incorporating into operable linkage a ~~first~~ DNA segment encoding a secretion signal, ~~operably linked to~~ a genomic DNA segment encoding an Aα chain of fibrinogen ~~into a β-lactoglobulin gene~~ and an additional segment required for expression of the Aα chain in the mammary gland of a mammal to produce a first gene fusion ~~comprising a β-lactoglobulin promoter operably linked to the first DNA segment~~;

incorporating into operable linkage a ~~second~~ DNA segment encoding a secretion signal, a genomic DNA segment encoding ~~operably linked to~~ a Bβ chain of fibrinogen ~~into a β-lactoglobulin gene~~ and an additional segment required for expression of the Bβ chain to produce a second gene fusion ~~comprising a β-lactoglobulin promoter operably linked to the second DNA segment~~;

incorporating into operable linkage a ~~third~~ DNA segment encoding a secretion signal, a genomic DNA segment encoding ~~operably linked to~~ a γ chain of fibrinogen and an additional segment required for expression of the γ chain ~~into a β-lactoglobulin gene~~ to produce a

third gene fusion, ~~comprising a β-lactoglobulin promoter operably linked to the third DNA segment~~ wherein each of said first, second and third segments are of the same species;

linking the first, second and third gene fusions in a single vector; introducing said first, second and third gene fusions into the germ line of a non-human mammal so that said DNA segments are expressed in a mammary gland of said mammal or its female progeny and biocompetent fibrinogen is secreted into milk of said mammal or its female progeny;

obtaining milk from said mammal or its female progeny; and

recovering said fibrinogen from said milk.

13. (original) A method according to claim 12 wherein said mammal is a sheep, pig, goat or cow.

14. (canceled)

15. (canceled)

16. (original) A method according to claim 12 wherein said introducing step comprises injecting said first, second and third gene fusions into a pronucleus of a fertilized egg and inserting said egg into an oviduct of a pseudopregnant female to produce female offspring carrying said gene fusions in the germ line, wherein said egg and said pseudopregnant female are of the same species.

17. (original) A method according to claim 12 wherein said mammal is a sheep.

18-22. (canceled)

23. (twice amended) A process for producing a transgenic offspring of a mammal comprising:

providing a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain, the DNA segment comprising genomic DNA encoding the Aα chain; a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, the DNA segment comprising genomic DNA encoding the Bβ chain; and a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, the DNA segment comprising genomic DNA encoding the γ chain; wherein each chain is derived from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal;

linking the first, second and third segments in a single vector;

introducing said DNA segments into an [fertilized] egg or an early stage embryo of a non-human mammalian species heterologous to the species of origin of said fibrinogen chains;

inserting said [fertilized] egg or early stage embryo into an oviduct or uterus of a female of said mammalian species; and

allowing said [fertilized] egg or early stage embryo to develop thereby producing transgenic offspring carrying said first, second and third DNA segments, wherein female progeny of said mammal express said DNA segments in a mammary gland to produce biocompetent fibrinogen.

24. (original) A process according to claim 23 wherein said offspring is female.

25. (original) A process according to claim 23 wherein said offspring is male.

26-33. (canceled)

34. (amended) A set of DNA sequences comprising:

a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain, the DNA segment comprising genomic DNA encoding the Aα chain;

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, the DNA segment comprising genomic DNA encoding the Bβ chain; and

a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, the DNA segment comprising genomic DNA encoding the γ chain, wherein each chain is from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal;

and the first, second, third segments are linked in a single vector.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

On _____

TOWNSEND and TOWNSEND and CREW LLP

By:_____
Susan J. Johnson

PATENT
Docket No.: 016994-018800US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 1781
Donna E. Prunkard, et al.	Examiner: D. Crouch
Application No.: 09/232,488	Art Unit: 1632
Filed: January 15, 1999	
For: PRODUCTION OF FIBRINOGEN IN TRANSGENIC ANIMALS	DECLARATION OF DONNA E. PRUNKARD AND DONALD C. FOSTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. We, the co-inventors of the above application, make this declaration as a supplement to our prior declaration of January 13, 1999.

2. We have reviewed the granted claims of US5,639,940, and the set of claims that were filed with the application. We understand that amendments relative to the originally granted claims are shown by underlining for additions and brackets for deletions. Every error in the patent which was corrected in the set of claims filed with the application including the reference to heterologous gene segments in claim 30 arose without any deceptive intention by us.

3. We have also reviewed the set of claims that are currently pending in the application. Again, we understand underlining and brackets are used to show additions and deletions relative to the original claims. Every error now being corrected in the present reissue application, and is not covered by our previous declaration, arose without any deceptive intention by us.

4. We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

_____ _____

Donna E. Prunkard Date

Donald C. Foster 12/21/06

Donald C. Foster Date

Liebeschuetz, Joe

From: JFLA (Jeff Landes) [landesj@zgi.com]
Sent: Tuesday, September 04, 2007 10:45 AM
To: dprunk
Cc: KIGO (Kim Goplen)
Subject: RE: fbgn patent

RE: Prunkard Declaration

Reissue Application Serial No.: 09/232,488

Production of Fibrinogen in Transgenic Animals

Our Ref. No.: 93-15R1

Donna:

Thank you for getting back to me re: this declaration. I appreciate your efforts.

I understand from our phone conversation and from the below email text that you did not actually make the single vector with the three genes inserts. I also understand from our phone call that what you did was clone out these three separate genes and insert them into three separate vectors along with the regulatory elements. Your concern, therefore, is that you did not perform every element of independent claims 1, 12, 23 and 34 because you personally did not make the single vector as claimed.

We are asking you to execute a declaration of inventorship. For this above referenced re-issue application, as in the original application that subsequently issued as a patent, we have made the legal determination that you are an inventor: more specifically, a joint inventor. Joint inventors need not work together, make the same type/amount of contribution or contribute to all of the subject matter of the claims. So, it is not necessary that you contribute to all of the claimed subject matter. Your contribution to, for example, the gene cloning and to the development of the expression vectors is sufficient inventive contribution to the pending independent claims.

Moreover, as both Joe Liebeschuetz and I have explained, there is not a requirement that you provide detailed examples for every element that is in a claim. As you will see in the following text of an email from Joe Liebeschuetz to you, there is adequate language in the specification to support the pending claims.

> Excerpts from patent:
>
> In view of the size of the fibrinogen chain genes it is most practical to prepare three separate expression units, mix them, and introduce the mixture into the host. However, those skilled in the art will recognize that other protocols may be followed. For example, expression units for the three chains can be introduced individually into different embryos to be combined later by breeding. In a third approach, the three expression

> units can be linked in a single suitable vector, such as a yeast artificial chromosome or phage P1 clone. Coding sequences for two or three chains can be combined in polycistronic expression units (see, e.g., Levinson et al., U.S. Pat. No. 4,713,339).
>
> It is preferred to obtain a balanced expression of each fibrinogen chain to allow for efficient formation of the mature protein. Ideally, the three expression units should be on the same DNA molecule for introduction into eggs. This approach, however, may generate technical problems at, for example, the injection and manipulation stages. For example, the size of fibrinogen expression units may necessitate the use of yeast artificial chromosomes (YACs) or phage P1 to amplify and manipulate the DNA prior to injection. If this approach is followed, segments of DNA to be injected, containing all three expression units, would be very large, thus requiring modification of the injection procedure using, for example, larger bore needles. In a more simple approach, a mixture of each individual expression unit is used.

Please know that we have made a legal determination that you are an inventor of the currently pending reissue claims. Given the above discussion, your previous discussions with Gary Parker and with Joe Liebeschuetz, and your and my earlier phone discussion, we have explained our reasoning as best we can. I am not sure what more we can say.

As you will also read in the above text, there is some urgency to having your executed declaration. So, please either execute the declaration and return it to my attention using the addressed/stamped envelope that was provided, or let me know via email or phone that you are refusing to execute this declaration. If I do not receive your executed declaration or your notice of refusal to execute by September 12, 2007, then I will assume that you have refused to execute the declaration. I will then proceed accordingly.

Please contact me if you have any questions.

Sincerely,

Jeff

Jeff Landes, Esq.

Senior Patent Counsel

ZymoGenetics, Inc.

1201 Eastlake Ave. East

Seattle, WA 98102

p: 206-434-3727

f: 206-442-6678

e: landesj@zgi.com

-----Original Message-----
From: dprunk [mailto:dprunk@comcast.net]

Sent: Wednesday, August 29, 2007 9:52 AM
To: JFLA (Jeff Landes)
Subject: fbgn patent

Hi Jeff,

I finally got the fbgn paperwork - it was sent Certified Mail and needed a signature and yesterday was the first chance I had to get to the post office.

The only sentence that concerns me is "linking the first, second and third gene fusions in a single vector". My concern is based on my understanding of what a claim represents. I've always thought that a claim stated what had been done. Last February, I asked the Pharming lawyer if he could clarify the definition of claim for me, but he never answered that email. So maybe you can clarify it for me. Can a claim include things that you might have done?

Please believe me when I say that I really do want to sign this, but I need to understand what I'm signing.

Donna

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office

on February 26, 2008.

TOWNSEND and TOWNSEND and CREW LLP

By: Susan J. Johnson

PATENT
Docket No.: 016994-018800US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 1781
Donna E. Prunkard, et al.	Examiner: D. Crouch
Application No.: 09/232,488	Art Unit: 1632
Filed: January 15, 1999	
For: PRODUCTION OF FIBRINOGEN IN TRANSGENIC ANIMALS	DECLARATION OF DONNA E. PRUNKARD AND DONALD C. FOSTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

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Donald C. Foster for and on behalf of Donna E. Prunkard

12/11/07
Date

Donald C. Foster

12/11/07
Date